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Study of the mechanism of cationic drug release increase coated with Surelease[®] after curing

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ABSTRACT

This paper describes the investigation of the release mechanism of the cationic drug coated with Surelease[®] after curing compared with nonionic and anionic drug. The release rate of cured propafenone hydrochloride pellets coated with Surelease[®] was increased significantly compared with uncured ones. The changes in release rate after seal-coating proved the migration of drug into the polymer film. Based on a comparative study of ammonia permeation tests and the impact of ammonia on drug with different properties, it was shown that the change in release of the cationic drug after curing was related to the combination of cationic drug and ammonia in Surelease[®]. Also, the scanning electron microscopy results showed that curing and dissolution can both prevent polymer film coalescence. During coating, the evaporated ammonia combined with the cationic drug and the polymer film coalesced. However, the combined ammonia could be decomposed during curing and interrupt the coalescence of the polymer-coat, leading to increased release. In an optimized process, the ammonia in the Surelease[®] can be evaporated quickly and the ionization of the drug will be reduced. All these factors can contribute to the formation of the polymer film.

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1. Introduction

Ethylcellulose (EC) is the most widely used water-insoluble polymer for film-coating [1–3]. EC is tasteless, odorless, and has the ability to form tough, flexible coatings. The organic solvent system causes environmental pollution and produces

residual toxic solvent and so most film coatings are water-based. The latex dispersion system is prepared by an emulsion polymer and in this system; polymers are in a colloidal dispersion. This system is unstable under different forms of stress, such as the presence of electrolytes, changes in pH and storage temperature, and high shearing forces. These stresses

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must be avoided to prevent the system from breaking down and undergoing coagulation. But the aqueous suspension system has the advantage of stickiness and a higher polymer content which can shorten the processing time. In current laboratory practice, Surelease® and Aquacoat® are two most popular aqueous ethylcellulose dispersions.

Compared with Aquacoat®, Surelease® has many advantages: plasticizers can be added during the preparation of Surelease®, and there is no need to add them before coating. Since the polymer film is formed during coating, no curing is needed after coating [4,5], which saves a lot of time during the manufacturing process. Sadeghi investigated the release of drug from pellets coated with Surelease® containing hydroxypropyl methylcellulose (HPMC) E15 [6,7]. Their results showed that the release rate of drug decreased as the coating load of Surelease® increased. Mingxing Zhang [8] (2005) prepared bilayer-pulsive pellets with Surelease® as the control layer and found no change in the release of theophylline from pellets coated with Surelease® after curing. In our study, the release rate of both NPS (anionic drug) and CBZ (nonionic drug) from pellets coated with Surelease® did not change after curing. However, Sadeghi [9] showed that diclofenac sodium was released slightly faster than metoclopramide hydrochloride at equivalent coating loads; changes in the release rates after curing were occurred for both metoclopramide hydrochloride and diclofenac sodium. In our research work, we illustrate the mechanism of release for different drug coated with Surelease® thoroughly, which is different from the reference [9]. It was reported that the slower release of metoclopramide hydrochloride may be due to the formation of a poorly soluble complex of the drug and the ammonium oleate with large molecular size. This interaction may also account for the differences in release characteristics of the drugs after curing. But in our research, the complex of the cationic drug and the ammonia could not decrease the drug release, and could be destroyed easily after curing. The coating film could be destroyed by the evaporated ammonia, at the same time, the drug returned cationic form, so the release was increased. And after curing, the film could be destroyed by the evaporated ammonia, thus, porous structure would be formed, at the same time, the drug returned cationic form, so the release was increased.

Moreover the succinic acid [10] and any other new concept [11] can deserve the drug release of Surelease. The drug release from Surelease coated pellets with high succinic acid to drug ratios and different coating levels can obtain an ever more constant rate and release rates. Some new concept adapting the copolymer to aqueous ethylcellulose dispersion also can be used to provide stable drugs release.

In general, there is no need to cure after coating by Surelease®. But the drug release would be increased when curing after coated by Surelease®. And, this occurs only in the cationic drug. The major objectives of the study described in this paper are to: (1) investigate whether there are significant changes in the release rates after curing of propafenone hydrochloride (PPF, cationic drug) pellets coated with Surelease®; and (2) examine the factors that may explain these changes. By comparing the influence of curing on the release of metformin (MET, cationic drug), naproxen sodium (NPS, anionic drug), and carbamazepine (CBZ, nonionic drug) pellets

coated with Surelease®, the interaction of the cationic drug with ammonia in Surelease® is suggested to be the reason for the changes in drug release.

2. Materials and methods

2.1. Materials

The following materials were used in this research: propafenone hydrochloride (Panya Chemical Co. Ltd, Shanghai China; PPF), metformin (Shandong Keyuan Pharmaceutical Co. Ltd, Jinan China; MET), carbamazepine (Hezhong Chemical Co. Ltd, Wuhan China; CBZ), naproxen sodium (Ruiteng Chemical Co. Ltd, Shanghai China; NPS), microcrystalline cellulose (Avicel PH101; FMC Ltd. Cork, Ireland), lactose (Beijing Fengli Jinjiu Commerce and Trade Co. Ltd, Beijing China), hydroxypropyl methylcellulose (HPMC, Methocel® E5, Colorcon; Orpington UK), ethylcellulose aqueous dispersion (Surelease® E-7-7050, Colorcon, Darford, Kent, UK), polyvinyl pyrrolidone K30, and sodium chloride (Bodi Pharmaceutical Co. Ltd, Tianjin China).

2.2. Preparation of drug-loaded pellets

The different drug-loaded pellets are listed in Table 1. Drugs and excipients were mixed by passing them through an 80-mesh sieve three times. Binder solution was added until a wet mass was formed and, then, the wet mass was extruded using a Granulator (JBZ-300, Yilia Research Institute, Liaoning, China) with a 1.0 mm screen at a rate of 58 rpm on a laboratory scale (100 g). After that, the extruded material was transferred to a spheronizer (JBZ-300, Yilia Research Institute, Liaoning, China). The final pellets were obtained following spheronization at a speed of 1000 rpm for 5 min. Finally, the pellets were dried at 40 °C for 12 h and then passed through a 16–24-mesh sieve.

2.3. Seal-coating of pellets with HPMC E5

HPMC E5 (2%, w/w) solution was prepared. A 20 g sample of drug-loaded pellets was transferred to the fluidized-bedded coater (Yilia Research Institute, Liaoning, China) and the coating levels were 2%, 4%, 6% by weight gain and then the pellets were stored overnight. The coating process conditions are listed in Table 2.

Table 1 – Composition of pellet cores.

Ingredient	Percentage (% w/w)			
	PPF	MET	NPS	CBZ
Drug	50	20	50	20
MCC	40	80	50	80
Lactose	10	—	—	—
Binder solution	1.5% w/v, aqueous solution of PVP K30	Water	10% w/v, aqueous solution of sodium chloride	3% w/v, aqueous solution of PVP K30

Table 2 – Coating conditions.

Conditions	Seal-coating	Polymer-coating
Inlet air temperature (°C)	30–35	35–40
Spray rate (ml/min)	0.7–0.9	0.7–0.9
Atomizing air pressure (MPa)	38.0	36.0
Spray pressure (MPa)	0.5–0.7	0.5–0.7

2.4. Polymer-coating of pellets with Surelease®

Surelease® was diluted to 15% and a 20 g batch of pellets, with or without seal-coating, was coated with the diluted Surelease® under the conditions given in Table 2. After coating, the pellets were further fluidized for 30 min to ensure that a film was formed.

2.5. Curing of the final pellets

Each batch of final pellets was cured at 40 °C or 60 °C for 12 h.

2.6. Dissolution study

The behavior of the pellets was evaluated by in vitro dissolution tests (USP 31 dissolution apparatus 1). at a temperature of 37 ± 0.5 °C. After this, an aliquot of the fluid was withdrawn at 1, 2, 4, 6, 8, 10, 12 h. The samples were analyzed by UV-spectrophotometry (RuiLi Analytical Apparatus Co. Ltd, Beijing China). The mean cumulative release of the drugs was investigated.

2.7. Assay of drug content

Weigh and fine powder not fewer than 20 times dose of pellets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg PPF to a 100 ml flask, diluted with alcohol and sonicated until the drug dissolved completely. Aliquots of the solution were filtered and the PPF contents were measured at 248 nm. MET, NPS and CBZ contents were also measured at 233 nm, 330 nm, and 285 nm, respectively.

2.8. Permeation of ammonia from the seal-coating

A solution of HPMC E5 5% (w/w) was uniformly spread onto a glass plate and dried at 40 °C for 12 h. Then, it was striped from the glass plate.

The seal film was placed over a watch-glass filled with ammonia. The pH of the test paper was used to determine whether ammonia could permeate the seal film.

2.9. Stability test after storage under ammonia-saturated conditions

PPF pellets cores and pellets coated with 10% Surelease® over a seal-coating of HPMC E5 and the pellets themselves were both stored in a desiccator under ammonia saturation for 12 h at room temperature. The PPF release from these two kinds of pellets was measured and compared with pellets coated with 10% Surelease® over a 6% seal-coating of HPMC E5 without any ammonia treatment.

2.10. Scanning electron microscopy (SEM)

Dissolution tests of the PPF pellets (coated with 10% Surelease®), uncured and cured, at 40 °C for 12 h were carried out for 2 h.

The surfaces of the four kinds of pellets (uncured and cured; before and after dissolution) were sputter-coated with gold-palladium and examined by scanning electron microscopy (Hitachi S-3400N Japan).

3. Results and discussions

3.1. The influence of curing on PPF pellets coated with Surelease®

Usually, the release rate decreases as the coating level increases. The release profiles for PPF pellets coated with Surelease® are shown in Fig. 1 (All the Figures were dealt with Excel). However, in Fig. 2 the release rate of the cured pellets increased markedly and the release rate of the pellets cured at 60 °C was much faster than those uncured. Their surface was changed by curing as show in Fig. 3. Usually the curing can result in further coalescence of the polymer particles and a reduction in drug release. According to the mechanism of the film formation of Surelease®, the theoretical coating temperature is 34–38 °C. During coating, the film formed, and curing is not necessary. Curing can contribute to the film formation and reduce the release rate. However, in our study, for PPF, the opposite release result was obtained after curing. The release of PPF from the cured pellets coated with Surelease® was significantly faster than that of the uncured ones.

3.2. The influence of curing on PPF pellets coated with Surelease® and seal-coating layer

Migration of the active drug through the coating material could lead to a porous structure, resulting in a change in the release rate. So such an interaction may affect the drug release. To avoid this migration, in our study, different levels of HPMC were applied as a seal-coating. The release results of the pellets coated with different levels of seal-coating and polymer-coat are shown in Fig. 4. As the levels of seal-coating

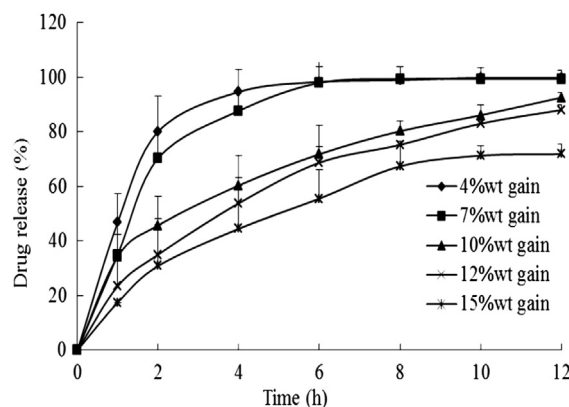


Fig. 1 – Release of propafenone hydrochloride with different coating levels of Surelease® (n = 6).

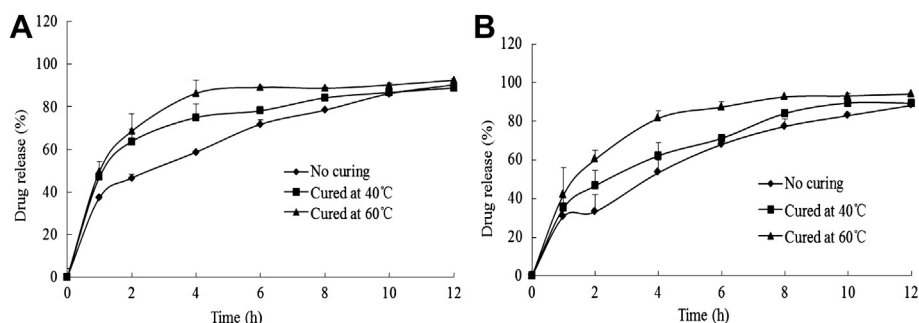


Fig. 2 – Influence of curing on the release of PPF pellets coated with Surelease® with weight gain of 10% (A) and 12% (B).

increased, the release decreased to the same rate. Although the dissolution results suggested that the seal-coating was unable to prevent the change in drug release after curing, the changes were not so marked as the load of seal-coating increased. However, under the different condition of curing (the temperature of curing was 40 °C and 60 °C), the release of the pellets coated with seal-coating was also markedly increased, as shown in Fig. 5. So, the seal-coating could not prevent the change in release of propafenone hydrochloride pellets coated with Surelease® after curing.

3.3. Permeation of ammonia from the seal-coating

After ruling out the possibility of the migration of the drug into the polymer-coating, the preparation process of Surelease® was investigated. Surelease® is a kind of aqueous ethylcellulose

dispersion, which was prepared by the phase transition method involving the melting of ethylcellulose and plasticizer (oleic acid) by heating. During the melting process, aqueous ammonia was added under high pressure. The aqueous suspension system was formed by phase transition. During the preparation, the plasticizer diffused into the polymer particles uniformly to increase the plasticity of the suspension system. After the phase transition, the plasticizer combined with ammonia can diffuse in the polymer in order to keep the polymer stable. So, there is no need to add the plasticizer while coating.

In order to determine the reason for the change in release, we examined the interaction between the drug and ammonium oleate in Surelease®. According to the mechanism of the film formation, during the coating process ammonia evaporates, leaving behind oleic acid rather than ammonium oleate. The oleic acid played the role of plasticizer, while the

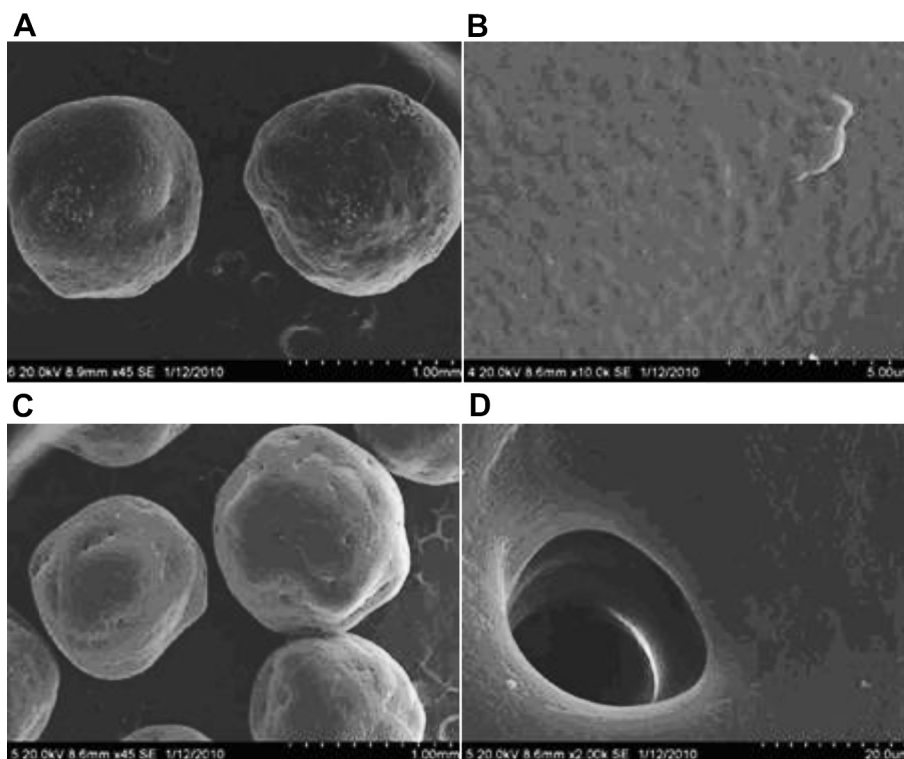


Fig. 3 – SEM photographs of PPF pellets (coated with 10% Surelease®) uncured (A: Magnification: 45; B: Magnification: 1000) and cured at 40 °C for 12 h. (C: Magnification: 45; D: Magnification: 1000).

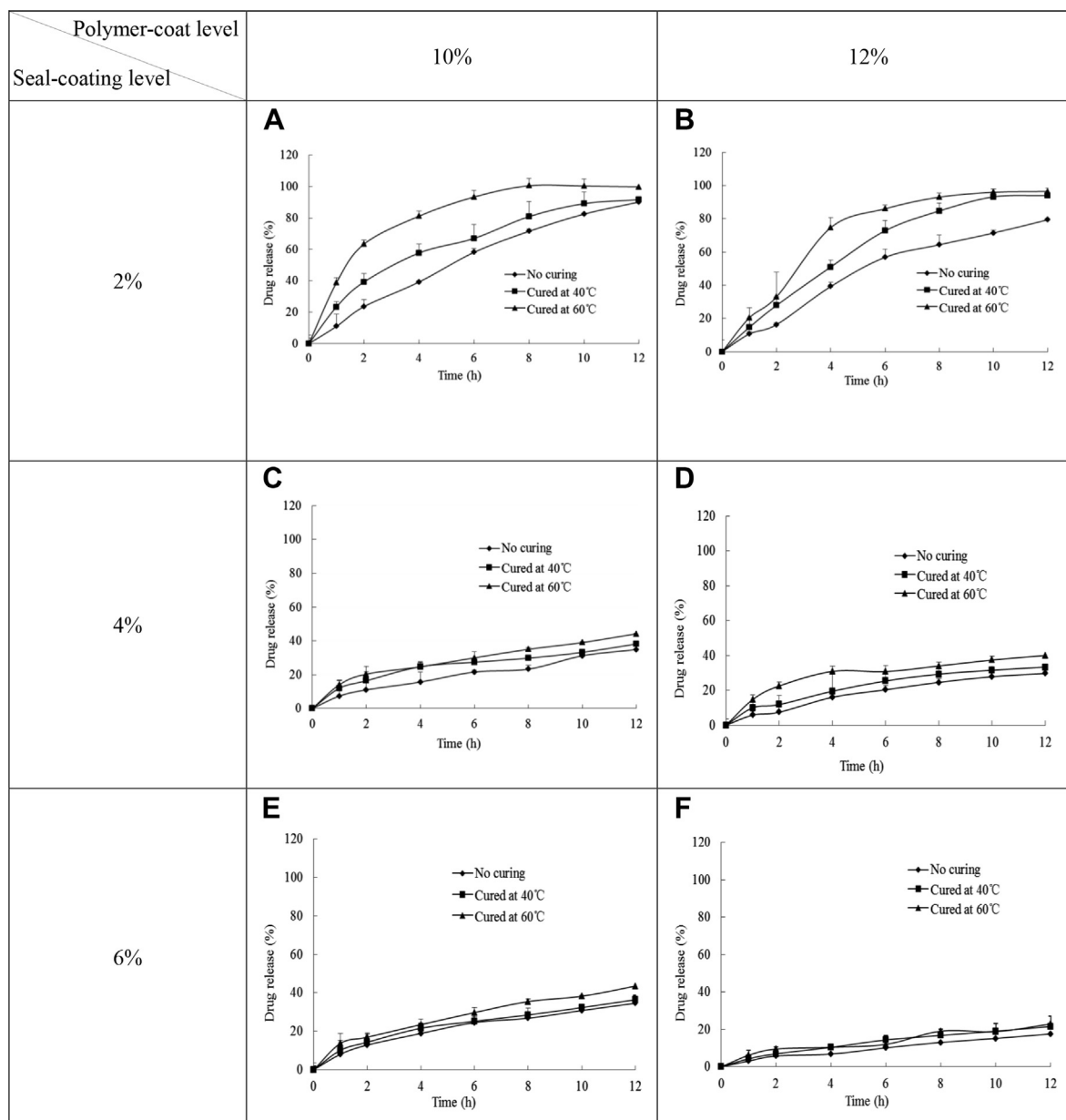


Fig. 4 – Influence of curing on drug release from different levels of seal-coating PPF pellets coated with Surelease®. (A) Polymer-coat level was 10% and seal-coating level was 2%; (B) Polymer-coat level was 12% and seal-coating level was 2%; (C) Polymer-coat level was 10% and seal-coating level was 4%; (D) Polymer-coat level was 12% and seal-coating level was 4%; (E) Polymer-coat level was 10% and seal-coating level was 6%; (F) Polymer-coat level was 12% and seal-coating level was 6%.

evaporated ammonia reduced the repulsion among the polymer particles. As the resistance decreased, polymer particles became closely packed and coalescence took place with the help of the plasticizer. During coating, if the drying was insufficient, the cationic drugs under moist conditions could become ionize cations, which can interact with ammonia. As shown in Fig. 3, the film of the uncured pellets coalesced completely. However, after curing at 40 °C, some pins appeared on the surface of the pellets, caused by the evaporated ammonia (Fig. 3). The difference between the cured and uncured pellets was clear after the dissolution test. Also, after the dissolution test, the film of the cured pellets split as shown in Fig. 6.

From the ammonia permeation test, the color of the allochromic pH test paper over the seal film changed to blue, which proved that ammonia was able to permeate the seal-coating during coating.

3.4. Interaction between ammonia and cationic drug

According to the theory of Lewis, all substances which can receive duplets are acids while all those which can provide duplets are alkalis. Therefore, the essence of the acid–base reaction can be summarized as the formation of a coordinate bond and production of a coordination compound. From the definition, the cationic drug can be taken as an acid and the

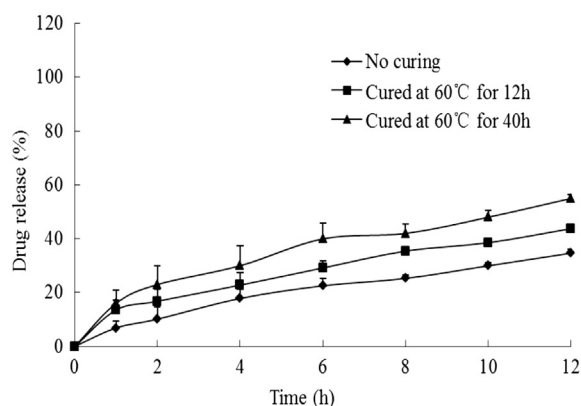
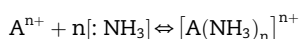


Fig. 5 – Influence of different curing times at 60 °C on drug release of PPF pellets coated with 10% Surelease® over 6% seal-coating.

ammonia can be taken as an alkali. So, the interaction of them can be summarized as follows:



This kind of coordination compound can be formed when the ammonia evaporates during the process of coating of the cationic drug pellets with Surelease®. At the same time, the polymer film is also formed as the ammonia evaporates, as shown by Fig. 3. The release of uncured pellets shows that the sustained characteristics of the film were very marked and the release decreased as the coating

level increased. However, after being cured, the release of the drug changed significantly. During the curing process, the ammonia of the coordination compound would be evaporated. For this reason, the film might be destroyed by the detached ammonia, thus, the drug release could increase. Each coordination compound has a formation constant (K), which is affected by a number of factors such as heating and oxidoreduction.

$$K = \frac{C_{[A(NH_3)_n]^{n+}}}{C_{A^{n+}} \cdot C_{[:NH_3]}^n}$$

During coating, there is a lot of ammonia in Surelease®, so the balance of the reaction would move to the right of equation, much poorly coordination compound were formed, that was, K was increased and the drug complex was decreased/increased. When cured after coating, ammonia moved to left, the coordination compound would decompose, the drug existed in the form of cationic, and the evaporated ammonia lead to porous structure on the surface, therefore, the drug release was increased.

3.5. Stability test after storage under ammonia-saturated conditions

To confirm this interaction, the storage stability under ammonia saturation was investigated. From Fig. 7, compared with the release of the three kinds of pellets, the release of the pellets treated with ammonia before coating was faster than that of the untreated pellets. The reason for this could be that during storage under ammonia saturation, ammonia could combine with the cationic drug and be

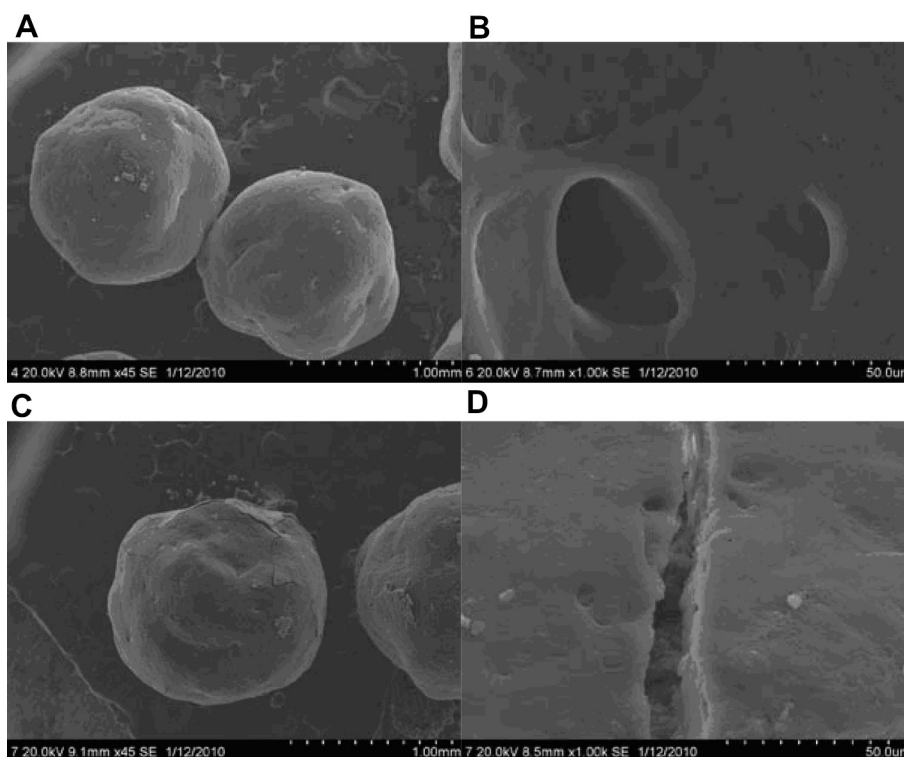


Fig. 6 – SEM photographs of PPF pellets (coated with 10% Surelease®) uncured (A) Magnification: 45 (B) Magnification: 1000 and cured at 40 °C for 12 h (C) Magnification: 45 (D) Magnification: 1000 after dissolution for 2 h.

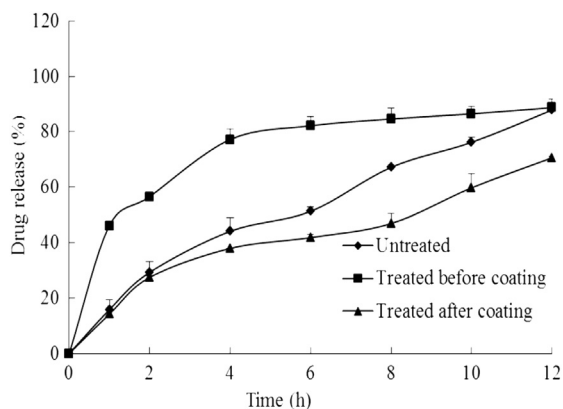


Fig. 7 – Influence of storage stability under ammonia-saturated conditions on drug release of PPF pellets coated with 10% Surelease® over 6% seal-coating.

delivered during coating, which would prevent coalescence of the polymer film. However, the release of pellets treated with ammonia after coating became slower, which could be due to the fact that the ammonia outside polymer-coat (HPMC) prevented the ammonia to deliver which was inside the polymer-coat. According to the equation, the ammonia which inside the polymer-coat was combination with the cationic drug to become poorly soluble complex $[A(NH_3)_n]^{n+}$, therefore, the drug could not release from the

pellets. So, the film could coalesce without the ammonia inside the polymer-coat. Therefore, the reason for the changed release of propafenone hydrochloride pellets after curing is due to the combination between the cationic drug and the ammonia of Surelease® during coating.

3.6. The influence of curing on another three kinds of drug pellets coated with Surelease®

In order to test the validity of this explanation, an investigation was performed to examine the influence of curing on the release of another three kinds of drug including MET (a water-soluble cationic drug), NPS (anionic drug), and CBZ (nonionic drug) from pellets coated with Surelease®. The results are shown in Fig. 8. The release rate of NPS and CBZ did not change after curing, which suggested that the film coalescence had taken place during coating. However, the release rate of MET from the pellets coated with Surelease® showed a marked increase after curing. Comparison of the results proved that only the cationic drug could cause a change in the release of pellets coated with Surelease® after curing. So, the reason for the rate change is the interaction of ammonia and the cationic drug.

3.7. The influence of coating conditions

The coating conditions of Surelease® are very important in our study. Possible reasons for this could be: firstly, the ammonia

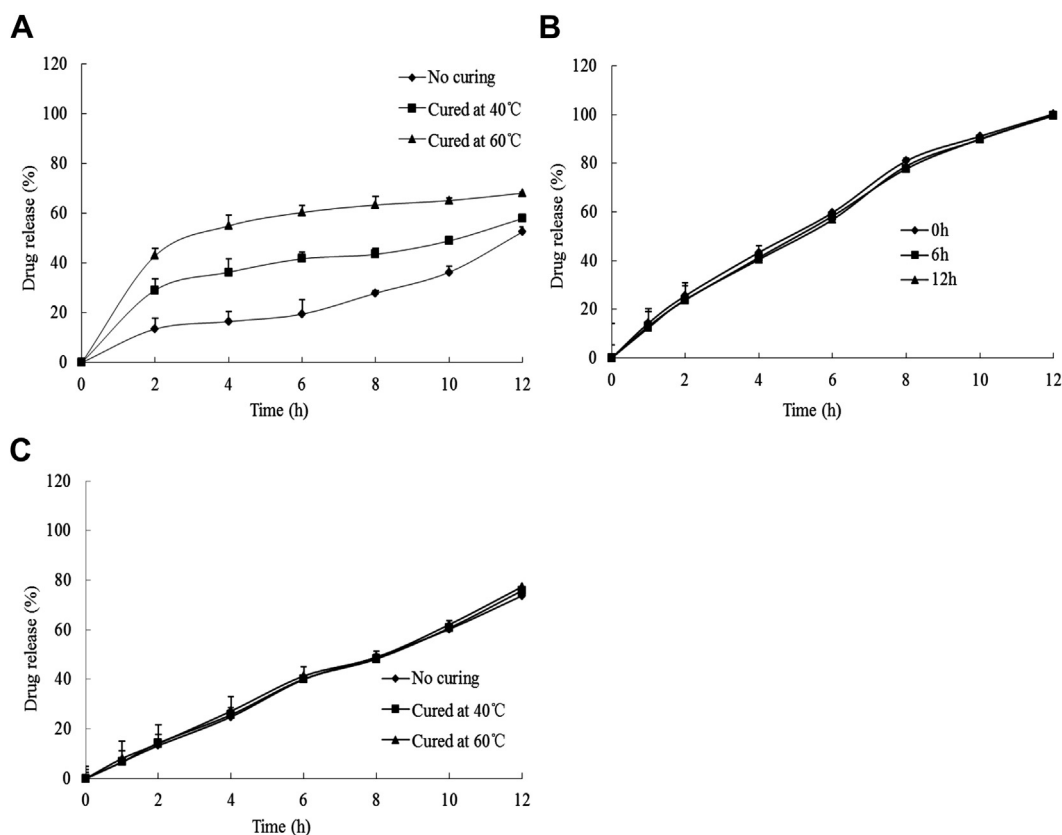


Fig. 8 – Influence of 12 h curing at 40 °C, 60 °C on the drug release of MET (A), NPS (B) and CBZ (C) pellets coated with 50% weight gain Surelease®.

needs to be evaporated during coating, which reduces repulsion among the polymer particles. Secondly, the optimized process provides sufficient drying, which can reduce the combination of the drug with evaporated ammonia during coating. Thirdly, the proper temperature during coating contributes to the polymer film coalescence without curing. The minimum film forming temperature of Surelease® (MFT) is about 23 °C and the coating temperature is around 35–40 °C or higher. And spray rate is 0.7–0.9 (ml/min) with atomizing air pressure 36.0 (MPa), with spray pressure 0.5–0.7 (MPa) or higher. The higher coating temperature and spray pressure can evaporate the ammonia during coating. Under optimized processing conditions, the film could be formed during coating and curing is not needed. The coating process needs to be optimized when Surelease® is chosen as the coating material.

4. Conclusions

Different from the anionic and nonionic drug, the cationic drug could cause a change in the release of pellets coated with Surelease® after curing. The change of release rate after curing is related to the combination between cationic drug and ammonia in Surelease®. And the combined ammonia can be decomposed easily during curing. In addition, no migration occurred during storage. Furthermore, the seal-coating could not prevent the change of drug release of pellets coated with Surelease® after curing. The coating process needs to be optimized when Surelease® is chosen as the coating material to obtain sufficient drying, which can reduce the combination of the drug with evaporated ammonia during coating without curing.

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